

Effect of oral garlic on arterial oxygen pressure in children with hepatopulmonary syndrome

Mehri Najafi Sani, Hamid Reza Kianifar, Abdolrazagh Kianee, Gholamreza Khatami

Mehri Najafi Sani, Gholamreza Khatami, Division of pediatric Gastroenterology, Department of Pediatrics, Children's Medical Center Hospital of Tehran University, Tehran, Iran

Hamid Reza Kianifar, Division of Pediatric Gastroenterology, Department of Pediatrics, Ghaem Medical Center of Mashhad University of Medical Sciences, Mashhad, Iran

Abdolrazagh Kianee, Division of Pediatric Cardiology, Department of Pediatrics, Children's Medical Center Hospital of Tehran University, Tehran, Iran

Correspondence to: Hamid Reza Kianifar, Division of Pediatric Gastroenterology, Department of Pediatrics, Ghaem Medical Center of Mashhad University of Medical Sciences, Ahmabad Ave, Mashhad, Iran. hr-kianifar@mums.ac.ir

Telephone: +98-511-7640815 Fax: +98-511-8417451

Received: 2005-10-09 Accepted: 2005-11-10

Najafi Sani M, Kianifar HR, Kianee A, Khatami G. Effect of oral garlic on arterial oxygen pressure in children with hepatopulmonary syndrome. *World J Gastroenterol* 2006; 12(15): 2427-2431

<http://www.wjgnet.com/1007-9327/12/2427.asp>

Abstract

AIM: To study the effect of oral garlic on arterial oxygen pressure in children with hepatopulmonary syndrome.

METHODS: Garlic powder in a capsule form was given to 15 children with hepatopulmonary syndrome (confirmed by contrast echocardiography) at the dosage of 1 g/1.73 m² per day. Patients were evaluated clinically and by arterial blood gas every four weeks.

RESULTS: The garlic capsule was administered to 15 patients with hepatopulmonary syndrome. There were 10 boys and 5 girls with a mean age of 9.4 ± 3.9 years. The underlying problems were biliary tract atresia (4 patients), autoimmune hepatitis (4 patients), cryptogenic cirrhosis (4 patients) and presinusoidal portal hypertension (3 patients). Eight patients (53.3%) showed an increase of 10 mmHg in their mean arterial oxygen pressure. The baseline PaO₂ was 65.6 ± 12.1 mmHg in the responder group and 47.1 ± 11.2 mmHg in non-responder group. At the end of treatment the mean PaO₂ in responders and non-responders was 92.2 ± 7.75 mmHg and 47.5 ± 11.87 mmHg, respectively (*P* < 0.01).

CONCLUSION: Garlic may increase oxygenation and improve dyspnea in children with hepatopulmonary syndrome.

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Key Words: Hepatopulmonary syndrome; Garlic; Arterial oxygen pressure; Pediatric

INTRODUCTION

In 1995, Lange *et al*^[1] introduced the term "hepatopulmonary syndrome" for those patients with pulmonary vasodilatation associated with chronic liver disease and cyanosis. Hepatopulmonary syndrome is defined by an arterial oxygen pressure < 70 mmHg in room air. In adults, the prevalence is 5%-29% and the overall mortality is 41% in hospitalized patients. In children, the prevalence ranges from 0.5% in those with portal vein obstruction to 20% in children with biliary atresia and polysplenia syndrome. In other causes of childhood cirrhosis, the prevalence is 2%-4%. Hepatopulmonary syndrome has been described in children as young as 6 months. Generally, hepatopulmonary syndrome is seen in chronic liver disease, but it has also been described in acute liver failure and extrahepatic portal venous obstruction^[2].

A right to left pulmonary shunt due to intrapulmonary vascular dilation characterizes this syndrome. Blood flowing through the dilated capillaries is less exposed to oxygen contained in the alveoli, resulting in a ventilation-perfusion mismatch^[3-6]. In animal models, elevated levels of nitric oxide have been detected in the lung homogenates of animals with the clinical features of hepatopulmonary syndrome. This finding appears to be supported by reports documenting increased exhaled nitric oxide concentration in patients with hepatopulmonary syndrome^[7,8].

The best method to evaluate the shunt in hepatopulmonary syndrome is the contrast-enhanced echocardiogram^[1,2,9,10]. Technetium 99m-labeled macroaggregated albumin scanning is a second method of detecting intrapulmonary vascular dilatations. Pulmonary arteriography can suggest two angiographic patterns^[1]. Schneck *et al*^[15] have reported the beneficial effect of methylene blue on this syndrome^[13]. The transjugular intrahepatic portosystemic shunt (TIPS)^[14], cavoplasty^[15], octreotide^[16], indomethacin^[17,18] and embolization^[19] in the management of this syndrome have been assessed.

In 1992, clinical improvement in a case report was

Table 1 Baseline characteristics of children with hepatopulmonary syndrome

	Age (yr)	Gender	Type of disease	Duration (yr)	Child score	Dyspnea
Non-responders	14	M	Cryptogenic cirrhosis	10	C	+
	10	M	AIH	5	B	-
	6	M	Biliary atresia	6	C	+
	3	F	Biliary atresia	3	C	+
	13	M	Presinusoidal	10	A	+
	12	F	Presinusoidal	9	C	+
	9	M	Biliary atresia	9	C	+
Responders	7	F	Cryptogenic	4	B	+
	12	M	Biliary atresia	11	C	+
	3	F	AIH	1	A	+
	14	M	Cryptogenic cirrhosis	9	B	+
	13	M	Presinusoidal	8	A	+
	4	M	AIH	1	A	-
	11	M	Cryptogenic cirrhosis	5	B	-
	11	F	AIH	5	A	-

AIH: Autoimmune hepatitis.

achieved following the use of garlic^[20]. In a study by Abrams *et al*^[21] the use of garlic in adults in treatment of this syndrome was evaluated and garlic was found to be an effective therapy for this syndrome especially in young groups. Ku *et al*^[22] revealed that active garlic metabolites are capable of pulmonary vasodilatation in rats. In 1997 Battaglia *et al*^[23] reported an improvement in right to left shunt and arterio-alveolar gradient in such patients after liver transplantation. Further studies have confirmed the beneficial effect of liver transplantation on this syndrome^[24, 25]. In our country, liver transplantation has a long waiting list. If the oral garlic can improve the arterial oxygenation and dyspnea, it may represent a palliative therapy for patients with hepatopulmonary syndrome awaiting liver transplantation.

MATERIALS AND METHODS

Patients

Fifteen patients (aged 6 months - 14 years) suffering from chronic liver disease, portal hypertension or cirrhosis and intrapulmonary shunt which were confirmed by saline contrast echocardiography were enrolled in this pilot study. Patients with congenital heart diseases, acute and chronic lung diseases and symptoms of severe gastritis, were excluded from the study. This study was performed at Children's Medical Center Hospital of Tehran University from 2002-2003.

Methods

Arterial blood gases were obtained from the radial artery in a sitting position at the same time and in the same room. Echocardiography with saline contrast was performed as previously described^[13]. The presence of air bubbles in the left heart between 3 and 6 cardiac contractions indicated

intrapulmonary shunt. Garlic was administered to the patients at the dose of 0.5-2 g/1.73 m² per day. We obtained a special kind of dried garlic (Hamedan city garlic), which was prepared in the form of 250 mg capsules by the hospital pharmacy.

The parents were asked to add the capsule or its content to their food once or twice a day at the recommended dose. We evaluated the patients every month. Clinical symptoms and signs, probable drug complication, and patient's compliance to the drug were asked in each visit. Arterial blood gas (ABG) was taken in the same condition as mentioned above. During the study we provided some facilities such as free contact if needed.

Response to garlic was defined as a 10 mmHg increment in the PaO₂ or when PaO₂ was more than 70 mmHg. Baseline and monthly data between responders and non-responders were analyzed statistically.

The Ethics Committee of Tehran University approved the protocol. The parents of the children gave their informed consent.

Statistical analysis

The results were expressed as mean \pm SD. Differences between two groups were evaluated by Fisher's exact test, Mann Whitney U and Wilcoxon rank-sum tests. $P < 0.05$ was considered statistically significant.

RESULTS

The baseline data of patients are summarized in Table 1. Fifteen patients with hepatopulmonary syndrome were treated with garlic. One child expired after one month of treatment.

At the end of the first month arterial O₂ pressure was increased significantly ($P = 0.004$). The mean of arterial O₂

Table 2 PaO₂ values of responders and non-responders in relation to dyspnea after treatment

Responders	Baseline	1 st mo	2 nd mo	3 rd mo	4 th mo	5 th mo	Dypnea after Rx
1	66	85	90	90	90	95	Improved
2	70	86	87	90	99	99	Worsened
3	74	83	85	90	90	95	Improved
4	59	79	85	95	99	99	Improved
5	43	77	79	80	80	80	Improved
6	63	85	95	95	95	95	^a
7	85	91	90	92	91	95	^a
8	65	69	76	84	82	80	^a
Non-responders							
1	34	33	32	35	40	40	No change
2	65	70	71	70	70	69	^a
3	51	55	54	55	40	40	Worsened
4	57	58	Worsened
5	37	42	40	39	45	47	No change
6	45	49	51	54	50	52	No change
7	40	35	37	41	39	37	Worsened

^aNo dyspnea before and after treatment.Table 3 PaO₂ values after oral garlic administration (mean ± SD, *n* = 15)

	Baseline	1 st mo	2 nd mo	3 rd mo	4 th mo	5 th mo
Non-responders	47.1 ± 11.2	48.8 ± 13.2	47.5 ± 14.2	49 ± 13.1	47.3 ± 11.8	47.5 ± 11.8
Responders ^b	65.6 ± 12.1	82 ± 6.8	85.8 ± 6.1	89.5 ± 5.1	90.7 ± 7	92.2 ± 7.7 ^d
Total	57 ± 14.7	66.5 ± 19.7	69.4 ± 22	72.1 ± 22.6	72.1 ± 24	73 ± 24.7 ^d

^b*P* < 0.01 vs non-responders, ^d*P* < 0.01 vs baseline.

pressure increment at the end of the second month was higher than 10 mmHg and over 70 mmHg at the end of the third month. At the end of the fifth month, the mean increment in the arterial O₂ pressure was 15 mmHg (Table 2).

Eight patients (53.3%) were considered as responders. The baseline PaO₂ was 65.6 ± 12.1 mmHg in the responder group and 47.1 ± 11.2 mmHg in non-responder group. There was a statistically significant difference in the initial O₂ pressure between the responders and non-responders (*P* = 0.009). At the end of treatment the mean PaO₂ in responders and non-responders was 92.2 ± 7.75 mmHg and 47.5 ± 11.87 mmHg, respectively (Table 3).

Dyspnea (including shortness of breath at rest or exercise, orthopnea and platypnea) occurred in 5 responders and 6 non-responders. Four out of these 11 patients had their dyspnea improved after treatment (Table 2).

According to the Child score, 5 patients (33.3%) were in group A, 4 (26.6%) in group B, and 6 (40%) in group C. The mean of arterial oxygen pressure in groups A, B and C, at the beginning of therapy was 56.4 ± 15.6 mmHg, 68.7 ± 11.2 mmHg and 49.6 ± 12.8 mmHg, respectively. At the end of therapy the mean PaO₂ in A, B and C groups was 79.4 ± 19.6 mmHg, 88.2 ± 13.3 mmHg and 53.6 ± 26 mmHg, respectively. No statistical difference in

the mean PaO₂ was noted between groups A, B, and C.

DISCUSSION

The role of garlic in the management of hepatopulmonary syndrome is controversial. In 1992, clinical improvement was reported following the use of garlic [20]. In 1998 Abrams *et al* [21] studied the effects of garlic on hepatopulmonary syndrome in adults [21]. Chan *et al* [26] showed that garlic has no effect on the improvement of PaO₂ and hypoxemia as well as clinical status, suggesting that deteriorating oxygenation in patients with chronic liver disease may be an indication for liver transplantation. Abrams *et al* [21] showed that 40% of patients have at least an increase of 10 mmHg in their arterial oxygen pressure after treatment with garlic. They also studied the dyspnea index in these patients and reported that all patients responding to therapy have an improvement in dyspnea [21]. In the present study, 53.3% of patients following the use of garlic had an arterial oxygen pressure > 70 mmHg or an increment > 10 mmHg. Four out of the 8 patients responding to the therapy had an improvement in dyspnea, but non-responders did not show any improvement in their respiratory symptoms.

It was reported that the clinical response is better in younger patients^[21]. The results of the present study are consistent with those of Abrams *et al*^[21]. We showed an improvement rate of 53.4% in children and Abrams *et al* showed 40% in adults. Nevertheless, no statistically significant differences were noted between responders and non-responders with respect to age.

It is interesting to note that responders had a higher baseline PaO₂, suggesting that non-responders have a severe and profound disease and that medical management can be effective when baseline PaO₂ is higher. Since TC-99 macro-aggregated albumin scan was not performed in the present study, there was a possibility of selection bias, because anatomic shunt failing to respond to medical therapy was not excluded.

The exact mechanism of garlic therapy for hepatopulmonary syndrome is not known. Garlic appears to cause pulmonary vasodilatation^[22] and increases the rate of NO synthesis^[25, 27, 28]. Thus one can conclude that garlic worsens hepatopulmonary syndrome. Garlic causes reduced NO synthesis in macrophages, resulting in reduced concentration in hypoxic tissue^[29].

Intrapulmonary vasodilatation occurs primarily in the bases of the lungs, resulting in significant V/Q mismatch in this region. Abrams *et al*^[21] speculated that if garlic results in uniform vasodilatation throughout the lung, then a redistribution of pulmonary blood flow to apical and mid lung fields could significantly improve V/Q ratios in these regions. Therefore, garlic may improve V/Q and reduce NO synthesis in the lung bases. Also garlic is known as a hepatoprotective agent and protects liver against tissue and chemical injuries. If this is the case, it is probable that garlic might improve liver function and hepatopulmonary syndrome. Garlic might also reduce portal hypertension, indirectly resulting in an improvement in hepatopulmonary syndrome. Additionally, Allicin, Ajoene, and diallyl sulfur may be beneficial for hepatopulmonary syndrome treatment. These ingredients are present in dried garlic in sufficient amount^[22]. However, the amounts of these ingredients vary depending on different types of garlic^[29].

In children with chronic cholestasis, repeated transcutaneous bedside measurements are a rapid and reliable noninvasive test for characterizing the severity of abnormal oxygenation, and may prove useful also in post liver transplantation monitoring^[30]. Although the existence of hypoxemia and hepatopulmonary syndrome has a prognostic value in patients with chronic liver disease^[31], controlling the oxygen pressure, is not recommended as a screening tool^[9, 10]. Therefore disease in diagnosis and control echocardiography with contrast should be more exact.

In conclusion, garlic can reduce the severity of hepatopulmonary syndrome. Arterial oxygen pressure is increased after treatment with garlic. Further studies are needed to evaluate the garlic therapy for hepatopulmonary syndrome in children.

ACKNOWLEDGEMENTS

The authors thank nurses of Gastroenterology and Cardiology Wards in Children's Medical Center Hospital and

also Miss. Khaef and Miss. Javadzadeh for their kind assistance in this study.

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S- Editor Wang J L- Editor Wang XL E- Editor Zhang Y